Summer 2013

Lebanon VAMC Pharmacy

Pharmacotherapy Update

Special points of interest:

- **New Drug in Pipeline**: review of a novel anti-diabetic medication currently in development
- Drug Information Corner: Use of Vitamin D for treating statin induced myalgias

Inside this issue:

Editor Notes

This is the final edition from the residency class of 2013 is full of enlightening information. Whether you plan to read this in your office or on the shore, you'll be sure to learn something new.

In this edition you will read about a novel anti-diabetes agent for the treatment of type II diabetes from one of our pharmacy students. Might be too early to tell if this agent will be a game changer, but you will have to make that determination yourself.

Then another drug information question has been answered by one of our first year residents. She will tell you about vitamin D supplementation for the treatment of statin induced myalgias.

Several questions will be answered about urine drug screening and the utility of these tests. A nice chart is also provided showing which agents can cause a false-positive on a urine drug screen.

Finally for a bit of fun, find out where our department used to work prior to working at the Lebanon VA Medical Center.

Ashley Dorward, PharmD
Brett Read, PharmD, editors

New Eye Clinic Procedure

Eye Clinic Lucentis Patient's Prescription Process

WHEN: Occurs on Monday mornings by 12:00 PM

PROCEDURE: The technician assigned to compounds in the morning is to take the Pharmacy Dispensing Order which eye clinic has sent down and check the Eye Clinic Bin to make sure all prescriptions are in the bin.

If a prescription is not in the eye clinic bin, the technician needs to check the window prescription pick up bins, ASU, and other appropriate bins for the prescription.

If the prescription is not in the bins the technician should ask the miscellaneous pharmacist to verify that the prescription was processed in VISTA. If the prescription has not been processed or not processed properly, the pharmacist will need to process/reprint the prescription. The technician will process the prescription through the Scriptpro system and then alert the set up pharmacist that the prescription goes in the eye clinic bin.

Once the technician ensures that all of the prescriptions are in the eye clinic bin, the technician should sign the form in the space **below** the "received by" block (not in the "received by" block) to signify that the prescriptions are all in the bin.

New Drug in the Pipeline

Imeglimin (POXEL®): A Novel Oral Agent for Type 2 Diabetes

By Lisa Mitchell, 2014 PharmD Candidate

Type 2 diabetes mellitus is a complex disease characterized by impaired insulin secretion and insulin resistance. Due to the progressive nature of the disease, pharmacotherapy is often necessary to attain glycemic control and prevent complications. Imeglimin is the first drug in a new class of oral antidiabetic agents, the Glimins. This agent works by inhibiting oxidative phosphorylation to inhibit hepatic glucose production, increase glucose uptake by peripheral tissues, and increase insulin secretion.

In a recent Phase IIa clinical trial, imeglimin was compared to metformin 850 mg BID over 4 and 8 week studies to determine efficacy with four different dosing strategies.

4-week Study:
•Type 2– diabetic patients who were treatment naïve or treated with antidiabetic monotherapy
•Randomized in a 1:1:1 ratio to receive either imeglimin 1000 mg BID (n=20), imeglimin 2000 mg once daily (n=20), or metformin 850 mg BID (n=19) following a 3-week washout period

8-week Study:
•Type 2– diabetic patients who were treatment naïve or treated with antidiabetic monotherapy
•Randomized in a 1:1:1:1 ratio to receive either imeglimin 500 mg BID (n=31), imeglimin 1500 mg BID (n=31), metformin 850 mg BID (n=33), or placebo (n=33) following a 3-week single blind washout/run-in period

The 4-week study, conducted in Germany, found significant elevations in first phase insulin secretion and reductions in plasma glucose for imeglimin 1000mg BID that were comparable to that of metformin. In the Imeglimin 2000mg once daily group, however, the effects were less significant compared to those of the Imeglimin 1000mg BID and metformin groups.

The 8-week study, conducted in Latvia, demonstrated similar results to the 4-week study. However, outcome measures including fasting plasma glucose and HbA1c were also assessed after 8 weeks. Imeglimin 1500 mg BID group resulted in reductions in both FPG and HbA1c that were comparable to the metformin group. Imeglimin 500 mg BID group, however, actually led to an increase in both glycemic parameters. These efficacy results demonstrate the importance of proper dosing and dosing separation to exhibit therapeutic benefit.

Compared to metformin, the imeglimin groups had significantly less total adverse events. No serious adverse events were reported with imeglimin. The most common adverse effects experienced included diarrhea, headache, abdominal pain, and microalbuminuria.

While this trial had some limitations – low baseline HbA1c, absent titration to maximum dose of metformin, employees and advisory board members for Poxel® (pharmaceutical company responsible for imeglimin) collecting and interpreting data— the promising efficacy and safety profile has led to the drug's progression into Phase IIb trials. Long-term data will be crucial in determining Imeglimin's place in current therapy practices.

References:

1.) Pirags V, Lebovitz H, Fouqueray P. Imeglimin, a novel glimin oral antidiabetic, exhibits a good efficacy and safety profile in type 2 diabetic patients. Diabetes Obes Metab. 2012; 14(9):852-8.

2.) Fouqueray P, Leverve X, Fontaine E, Baquié M, Wollheim C, Lobvitz H, Bozec S. Imeglimin- a new oral anti-diabetic that targets the three key defects of type 2 diabetes. J Diabetes Metab 2011;2(126):1-8

Drug Information Corner:
Evidence of Vitamin D for the treatment of statin-induced myalgias

By Megan Sculley, PharmD

Question:
What is the evidence behind using vitamin D for treatment of statin-induced myositis/myalgias?

Answer:
HMG-CoA reductase inhibitors, commonly known as statins, are used for hyperlipidemia and for primary and secondary prevention of cardiovascular disease. Unfortunately, statins are often discontinued by patients due to bothersome myalgias. Statins are discontinued in about 10% of patients after 1 year and about 28% of patients after 4 years—39% of those discontinuing therapy is due to adverse events. This can become an issue, especially in patients who are at very high risk for cardiovascular events—those patients that would likely benefit the most from a statin. In recent years, healthcare professionals have taken a special interest in understanding the mechanism behind statin-induced myopathy, and have been exploring ways to decrease that particularly rate-limiting side effect.

Possible mechanisms of myopathy include reduced coenzyme Q10 synthesis (renal failure, obstructive liver disease, and hypothyroidism) and vitamin D deficiency. The latter has been studied in diabetic patients, where a deficiency may lead to neuropathic pain; however, little is known about the relationship between vitamin D deficiency and statin-induced myalgia. Vitamin D deficiency is independently associated with muscle pain (at levels < 20ng/mL), which represents a possible underlying cause of statin-induced myalgia. A case series published in Clinical Endocrinology in 2009 did just that. 8 out of 11 patients with myalgias were vitamin D deficient, and the myalgias were resolved with cessation of the statin and supplementation of vitamin D. 4 out of 6 patients who were rechallenged with a statin after repletion of vitamin D reported statin tolerance for at least 6 months. The authors' conclusion of this study was that "..a direct contribution of vitamin D deficiency to the development of statin-induced muscle injury cannot be excluded." Whether there is a causative relationship between the statin and vitamin D level is unknown, however it is unlikely since atorvastatin has been associated with increased vitamin D levels. A second study by Ahmed et al. gave patients who were vitamin D deficient (levels <32 ng/mL) ergocalciferol 50,000 units x 12 weeks. 35 out of 38 patients has resolution of their myalgias after vitamin D repletion. 82 out of 128 total patients with myalgias on a statin were found to be deficient in vitamin D (mean level 20.8 ng/mL). Overall, this study concluded that vitamin D deficiency reversibly augments statin-induced myalgias.

The mechanism behind the interaction between vitamin D and statins lies in the CYP3A4 metabolic pathway as well as the muscle cells themselves, which supposedly contain vitamin D receptors themselves. The statins that are most commonly associated with myalgia (simvastatin and atorvastatin) inhibit CYP3A4. In vitamin D deficient states, the body uses the CYP3A4 pathway to convert inactive vitamin D to the active form via hydroxylation. With inactive vitamin D acting as a substrate of CYP3A4, it leaves less receptors to metabolize the statin, increasing the levels in the body and thus the risk for myalgias.

References:

1. Riphagen IJ, van der Veer E, Muskiet FA, Dejongste MJ. Myopathy during statin therapy in the daily practice of an outpatient cardiology clinic: prevalence, predictors and relation with vitamin D. Curr Med Res Opin. 2012 Jul;28(7):1247-52.
2. Reinhart KM, Woods JA. Strategies to preserve the use of statins in patients with previous muscular adverse effects. Am J Health Syst Pharm. 2012 Feb 15;69(4):291-300.
3. Kurnik D, Hochman I, Vesterman-Landes J, et al. Muscle pain and serum creatine kinase are not associated with low serum 25(OH) vitamin D levels in patients receiving statins. Clin Endocrinol (Oxf). 2012 Jul;77(1):36-41.
4. Glueck CJ, Abuchaibe C, Wang P. Symptomatic myositis-myalgia in hypercholesterolemic statin-treated patients with concurrent vitamin D deficiency leading to statin intolerance may reflect a reversible interaction between vitamin D deficiency and statins on skeletal muscle. Med Hypotheses. 2011 Oct;77(4):658-61.
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7. Gupta A, Thompson PD. The relationship of vitamin D deficiency to statin myopathy. Atherosclerosis. 2011 Mar;215(1):23-9.
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Farewell PGY1 Pharmacy Residents! Where will they be going next?

Ashley Dorward
New Position: PGY-2 Internal Medicine Specialty Residency
Location: Kaleida Health Center, Buffalo, NY

Jamie Kinscherff
New Position: Outpatient Pharmacist
Location: Southern Arizona VA Healthcare System (SAVAHCS), Tucson, AZ

Megan Sculley
New Position: PGY-2 Pain and Palliative Care Specialty Residency
Location: SUMMA Health System, Akron, OH

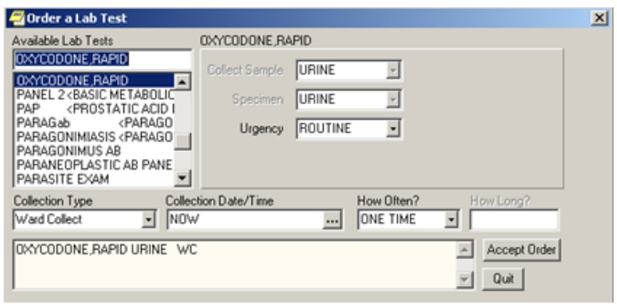
Urine Drug Screening at Lebanon VAMC (continues on pg. 6)

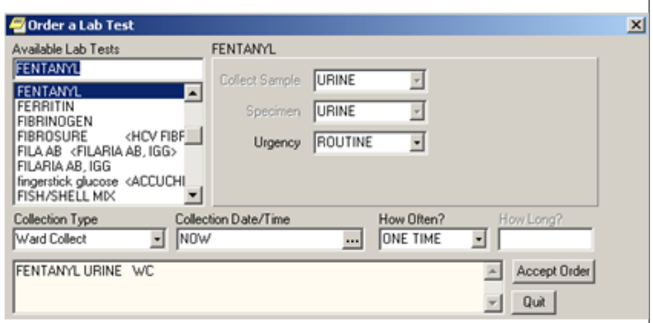
Urine Drug Screens (UDS) are an effective tool used to assess medication adherence, diversion and abuse. Although blood tests can also be used to detect the presence of drugs, urine is often the most preferred due to ease of sample collection, longer duration of positive results as well as high concentrations of drugs in urine.

At the Lebanon VA Medical Center, a UDS tests for the following substances:

- Amphetamines
- Barbiturates
- Benzodiazepines
- Cannabinoid
- Ethyl alcohol
- Methadone
- ***Opiates (morphine, codeine, and heroin)***
- PCP

*For UDS, to test for Oxycodone and/or Fentanyl, a specific "confirmatory test" must be ordered for each of these medications. This can be found in CPRS, as shown below





What Were They Doing *BEFORE* Pharmacy??

1. Eric Nerino _____
2. Michelle Kressler_____
3. Brett Read_____
4. Jamie Kinscherff_____
5. Carol Kercher_____
6. Inga Washington_____
7. Michele Margut_____
8. Sonia Martin_____
9. Tony Sniechoski____
10. Megan Sculley_____
11. Ashley Dorward_____
12. Kevin Koons_____
13. Dina Norris_____
14. Tara Muzyk_____
15. Jen Lutz_____
16. Steve Harkaway_____
17. Keith Vinglinsky_____
18. Allen Ayala_____
19. Ed Caudill _____
20. Lou Portas_____

A. Mason tender

B. Swimming pool salesman

C. Worked at Carvel Ice Cream

D. Large print operator (for wrestling singlet's)

E. 4th grader teacher

F. Landscape architecture

G. House boy at Chi Omega

H. Telephone operator

I. Waitress at Chilis Bar & Grill

J. Racecar Driver

K. Jazzercise

L. Orchard Worker (picked fruit)

M. Line crew at airport

N. Secretary at Geotechnical Engineer company

O. EKG Tech

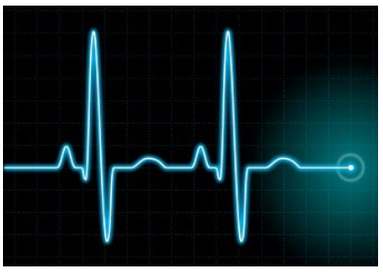
P. Bouncer

Q. Spiegel's Ordering Catalog

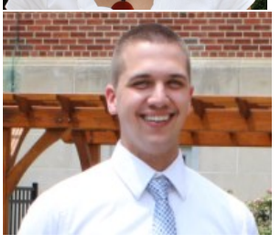
R. Worked in a scrap yard

S. Nursing/phlebotomist

T. Lifeguard



1. F , 2. S, 3. G, 4. E, 5. J, 6. N, 7.C, 8. Q, 9. R, 10.D, 11. I, 12. M, 13. T, 14. K, 15. H, 16. A, 17. B, 18. O, 19. L, 20. P



Goodbye, Lebanon!
THANKS for a great year!

Continued from page 4: Urine Drug Screening– False Positives

Drug	Urine Detection	Drugs Causing False (+)
Hydrocodone	1-2 days	n/a
Oxycodone	1-3 days	n/a
Hydromorphone	1-2 days	n/a
Morphine	3-4 days	Rifampin, fluoroquinolones (ciprofloxacin, levofloxacin), poppy seeds, dextromethorphan, diphenhydramine, quinine
Codeine	1-3 days	Rifampin, fluoroquinolones (ciprofloxacin, levofloxacin), poppy seeds, dextromethorphan, diphenhydramine, quinine
Heroin	2 days	Rifampin, fluoroquinolones (ciprofloxacin, levofloxacin), poppy seeds, dextromethorphan, diphenhydramine, quinine
Phencyclidine (PCP)		Venlafaxine, dextromethorphan, diphenhydramine, imipramine, ibuprofen
Methadone	5-10 days	Clomipramine, chlorpromazine, diphenhydramine, doxylamine, quetiapine, verapamil
Amphetamine	2-4 days	Ephedrine, pseudoephedrine, methylphenidate, phenylephrine, selegiline, trazodone, bupropion, desipramine, amantadine, ranitidine, labetalol
Methamphetamine	2-4 days	Same as amphetamine
Cannibinoids	2-4 days (up to 3 weeks)	NSAID's, efavirenz, hemp seed oil, dronabinol, PPI's
Benzodiazepine •Short-acting (lorazepam)	3 days	Sertraline, oxaprozin
Benzodiazepine •Long-acting	30 days	Sertraline, oxaprozin
Barbiturates	1 day-3 weeks	NSAID's

References:

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3. Standbridge JB, Adams SM, Zotos AP. Urine drug screen: a valuable office procedure. Am Fam Physician. 2010;81(5):635-640.
4. Vincent EC, Zebelman A, Goodwin C. What common substances can cause false positives on urine drug screens for drugs of abuse? J Fam Pract. 2006;55(10):893-897.